REMARKS

This Amendment is submitted in response to the April 15, 2009 Final Office Action issued by the United States Patent and Trademark Office. Applicant's representative wishes to take this opportunity to express his appreciation for the courtesy extended by Examiners Jon Weber and Bin Shen during a May 5, 2009 telephone conference. During the telephone conference agreement was reached that the above-recited claims would be allowable over the McMahon reference. Such agreement was confirmed in the May 12, 2009 Interview Summary prepared by Examiner Shen.

Support for new claims 30-33 may be found throughout the specification. Support for new claims 30-33 will be discussed in more detail below. No new matter is introduced by the addition of new claims 30-33. Since agreement was reached that new claims 30-33 above would be allowable, applicants respectfully request entry of this Amendment. Upon entry of this Amendment new claims 30-33 will be pending in the instant application.

Rejection of Claims Under 35 U.S.C. §103

In the April 15, 2009 Final Office Action, the Examiner rejected previously pending claims 26-29 under 35 U.S.C. §103 based on the McMahon reference. Applicant traverses this rejection.

Claims 30 and 31 are the only currently pending independent claims and recite, respectively:

> A method of treating a hypertensive subject having a normal to above normal plasma renin activity level comprising:
>
> A. administering to the subject or instructing the subject to take a low dose of an R drug;

B. after step A, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the R drug;

C. after step B, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take, instead of the R drug, a low dose of a V drug; and

D. after step C, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the V drug,

wherein said subject has been taking at least one anti-hypertensive drug and does not discontinue use of the at least one anti-hypertensive drug prior to measuring the normal to above normal plasma renin activity level.

* * *

A method of treating a hypertensive subject having a normal to below normal plasma renin activity level comprising:

A. administering to the subject or instructing the subject to take a low dose of an V drug;

B. after step A, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the V drug;

C. after step B, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take, instead of the V drug, a low dose of a R drug; and

D. after step C, measuring the subject's BP and if the subject's BP is not controlled, administering to the subject or instructing the subject to take an increased dose of the R drug,

wherein said subject has been taking at least one anti-hypertensive drug and does not discontinue use of the at

least one anti-hypertensive drug prior to measuring the normal to below normal plasma renin activity level.

During the May 5, 2009 telephone conference agreement was reached among Examiners Weber and Shen and applicant's representative that McMahon clearly teaches away from the presently pending claims in at least the following respect. McMahon at page 3 states that "[p]atients must be taken off all antihypertensive drugs for at least two weeks because these drugs greatly affect the PRA levels." (emphasis supplied) Since the above-recited independent claims make clear that the present invention does not require discontinuing use of all antihypertensive drugs, applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

For the sake of completeness applicant notes that the pending claims are further distinguishable from McMahon in at least three additional respects. (See Applicant's August 22, 2008 Amendment for additional details.) First, McMahon discusses several other perceived drawbacks in the use of PRA levels to guide a course of treatment, such as a lack of accurate assays, collection of 24-hour urine quantitatively, and the cost of such tests. (See McMahon, p. 3-4.) Second, given these perceived drawbacks, McMahon argues that the Joint National Committee guidelines should be followed whereby hypertensive patients should be treated initially with a diuretic rather than directing a course of treatment based on PRA levels. (See McMahon, p. 4) Third, McMahon states that high renin essential hypertension would likely require a second or even a third drug in contrast to the monotherapy treatment achievable in a large majority of subjects utilizing applicant's claimed methods. (See McMahon p. 5.)

Thus, these additional reasons, while not necessary for allowance, nevertheless provide further distinctions between McMahon and the pending claims.

Accordingly, for all of the reasons given above, applicant respectfully requests that the Examiner withdraw the rejection under 35 U.S.C. §103.

Support for New Claims 30-32

In the April 15, 2009 Final Office Action, the Examiner did not reject the claims based on 35 U.S.C. § 112, first paragraph. Nevertheless, for the sake of completeness, applicant provides below selected, non-exclusive excerpts from the specification which support the new language included in the presently pending claims.

It should be noted that one of the major advantages provided by the presently claimed invention, and discussed in detail in applicant's specification, is the ability to immediately begin directing a logical course of treatment for any given hypertensive subject based on an initial PRA measurement. The subject's plasma renin level can be measured immediately without discontinuing use of a hypertensive drug, much less discontinuing for "at least two weeks" as taught by McMahon. In contrast to McMahon, no delay is required and a rational course of treatment can be immediately started. For the Examiner's convenience all cites to paragraph numbers refer to applicant's published application 2005/0090752. The citations provided below refer to a subject already taking at least one anti-hypertensive drug prior to measurement of the subject's plasma renin activity level.

First, under the heading "Protocol II: Using Plasma Renin Activity (PRA) to Guide Treatment of Unsuccessfully Treated Patients" (at paragraph 111), the specification states at paragraphs 112 and 113:

> As indicated by FIG. 5 and Table 7 below, another exemplary embodiment of the Laragh Method is quite useful for determining which drug or drugs to select for the previously unsuccessfully treated hypertensive patient. The Laragh Method can be used for (a) patients on one or more V drugs, (b) patients on one or more R

> drugs, or (c) patients receiving one or more R and V drugs. As was the case for Protocol I, an exemplary embodiment of Protocol II may comprise a series of steps or visits.
>
> Visit 1 (as in Protocol I) may comprise measuring BP and drawing blood to test PRA levels. The appropriate action to take during Visit 2 is dependent on the PRA level. If the PRA level is below 0.65 ng/ml/hr and the patient is on a V drug alone, the patient may be treated consistent with the V side of Protocol I (FIG. 4), Visit 3 or 4. If the PRA level is below 0.65 ng/ml/hr and the patient is on an R drug alone, the R drug may be discontinued and treatment with a V drug initiated. This patient in Visit 3 will have his or her BP checked. If BP is controlled, subsequent visits will comprise routine follow-up. If BP is not controlled, the patient may be treated consistent with the V side of Protocol I, Visit 3. If the PRA level is below 0.65 and the patient is on both a V and R drug, the patient should be treated consistent with Protocol 1, Visit 6.

Thus, subjects already on one or more V or R or V and R drugs can have their PRA levels measured without having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Second, under the heading "Protocol IIA: For Unresponsive Hypertensive Patients Already Taking V Drug(s)" (at paragraph 116) the specification states at paragraphs 117 and 118:

> In more general terms, as shown in FIG. 5 and Table 7, the Laragh Method provides that a patient still in the titration phase of a single V drug should have the dose of the drug increased to a maximum level as long as the PRA remains below 0.65 ng/ml/hr. In such a patient the sodium volume factor is still operative and contributing to the hypertensive state. Since a renin factor is unlikely to be present in any patient with a low renin level, a patient on any V drug who remains hypertensive with a PRA level less than 0.65 ng/ml/hr is unlikely to respond to any R drug. Therefore, if a full dose of a V drug has already been tested, and assuming good compliance, a V drug with a different mechanism of action should be added. Thus, an exemplary embodiment of the Laragh Method provides that a diuretic can be added to a SARA or vice versa, and

> then an alpha blocker or CCB, could be added to a diuretic or SARA.
>
> Irrespective of whether the hypertensive patient is untreated or treated with a V drug, the higher the PRA level the more likely the patient is to have a renin component to the hypertension. If such an unresponsive patient is already on a full dose of V drug, the Laragh Method provides that an R drug should be added if the patient's PRAlevel is equal to or greater than 0.65 ng/ml/hr. However, if the patient's PRA is equal to or greater than 6.5, the Laragh Method directs that diuretics should be stopped and an R drug started because such high renin levels indicate some dehydration.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Third, under the heading "Protocol IIB: For Unresponsive Hypertensive Patients Already Taking R Drug(s)" (at paragraph 119) the specification states at paragraphs 120 and 121:

> Since a renin factor is unlikely to be present in any treated patient with a low renin level (except one treated with a beta blocker), an exemplary embodiment of the Laragh Method provides that any patient on a full dose of a CEI or ARB with a PRA level less than 0.65 ng/ml/hr who remains hypertensive should be switched a V drug.
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> According to an exemplary embodiment of the Laragh Method, a patient with a PRA equal to or greater than 0.65 ng/ml/hr who is unsuccessfully treated with a full dose of any R drug (CEI, ARB or beta blocker) should then have a V drug added as long as PRA is less than 6.5 ng/ml/hr. At or above this level the patient should be treated with a second R drug because, although the three classes of R drugs all block the renin-angiotensin system, they have different sites of action and may be additive for increasing inhibition of the renin system.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Fourth, under the heading "Protocol IIC: For Unresponsive Hypertensive Patients Already Taking One or More R and V Drugs" (at paragraph 122) the specification states at paragraphs 123:

> According to an exemplary embodiment of the Laragh Method as indicated in FIG. 5 and Table 7, a PRA test on the first visit is extremely helpful in this situation because it can reveal which mechanism predominates. Thus, PRA values less than 0.65 clearly indicate a sodium-volume excess is present and the patient should be treated as having a primary volume problem. The R drug should be stopped and a second V drug added. Conversely, if the PRA is between 0.65 and 6.5, the anti-renin limb of treatment needs to be strengthened by the addition of a second R drug. Above 6.5 ng/ml/hr, the V drug should be stopped because it may be causing excessive reactive renin secretion. A second R drug can be added, if necessary.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Fifth, paragraph 124 states:

> Thus, to summarize, the strategy dictated by an exemplary embodiment of the Laragh Method is to strengthen the V limb for PRA less than 0.65 and stop the anti-renin drugs. When the PRA is between 6.5 and 0.65 an R drug should be added. However, for those patients with PRAs equal to or greater than 6.5, the diuretic therapy should be stopped when the R limb is strengthened because such high renin values are usually associated with sodium volume depletion and overly reactive renin secretion.

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Sixth, paragraph 129 states:

> Patients with PRA levels above 6.5 ng/ml/hr on V drug(s) may have had a large reactive rise in PRA with the diuretic. If an R drug is added they are likely to have an even greater rise in PRA levels which could overwhelm the effects of anti-renin system blockade. In them the V drug should be stopped when the R drug is started. It is possible that such patients may eventually need a second R drug to completely control their BP (dotted arrow).

Thus, subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can then be based on the results of PRA measurements. Additional PRA measurements can be made to further refine the course of treatment.

Seventh, paragraph 136 states:

> The Laragh Method as applied to the evaluation and treatment of hypertensive crises is superior to traditional strategies which focus entirely on blood pressure correction per se, perhaps on the assumption that this is the only relevant traditional target. Traditional strategies, however, are faulty because they fail to promptly identify the causal mechanisms, while embodiments of the present invention allow prompt identification of causal mechanisms by immediately exploiting plasma renin testing and the blood pressure responses to specific pharmacologic probes to target causal mechanisms for more specific corrective drug treatments.

Again subjects already on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can be determined immediately.

Eighth, paragraph 137 states:

> Thus, in contrast to the Laragh Method, the traditional recommended approaches have relied heavily on I.V. nitroprusside … or oral calcium channel blockers, either of which are seductive because they will in fact at least partially reduce the high blood pressure immediately. But at the same time, whenever there is no mechanistic diagnosis, precious time is lost which could have been used to gain vital diagnostic information about the basic causal mechanisms involving renin-angiotensin and sodium-volume mechanisms.

Thus, subjects who may already be on one or more V or R drugs can have their PRA levels measured without having to having to discontinue use of a hypertensive drug. The course of treatment can be determined immediately.

Accordingly, as evidenced by the eight representative, non-exclusive excerpts from the specification referenced above, the language of the pending claims is fully supported by the specification. More specifically, as shown by these excerpts and elsewhere, the specification teaches that certain embodiments of the invention allow for the immediate use of PRA levels to direct a course of treatment without the need for having to discontinue use of a hypertensive drug for a protracted period.

Conclusion

In view of the foregoing, applicant respectfully requests that the Examiner allow the presently pending claims, namely claims 30-33.

No fee is believed to be necessary in connection with the filing of this Amendment. If any fees are deemed necessary by the Examiner, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-0540.

If a telephone interview would be of assistance in advancing prosecution of this application, applicant's undersigned attorney encourages the Examiner to telephone him at the number provided below.

Respectfully submitted,

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/Robert E. Alderson/

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